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The Impact of Mild Traumatic Brain Injury on Cognitive Functioning Following Co-occurring Spinal Cord Injury

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Abstract

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Meta-analytic studies have shown that mild traumatic brain injury (MTBI) has relatively negligible effects on cognitive functioning at 90 or more days post-injury. Few studies have prospectively examined the effects of MTBI in acute physical trauma populations. This prospective, cohort study compared the cognitive performance of persons who sustained a spinal cord injury (SCI) and a co-occurring MTBI ($N = 53$) to persons who sustained an SCI alone ($N = 64$) between 26 and 76 days (mean = 46) post-injury. The presence of MTBI was determined based on acute medical record review using a standardized algorithm. Primary outcome measures were seven neuropsychological tests that evaluated visual, verbal, and working memory, perceptual reasoning, and processing speed that controlled for potential upper extremity impairment. Persons who sustained SCI with or without MTBI had lower than expected performance across all neuropsychological tests, on average about 1 *SD* below the mean. Analysis of covariance indicated that persons with MTBI did not evidence greater impairment on any neuropsychological test. The aggregated effect size (Cohen's *d*) was −0.16. The strongest predictors of neuropsychological test scores were education, race, history of learning problems, and days from injury to rehabilitation admission. MTBI did not predict performance on any neuropsychological test. These findings are consistent with other controlled studies that indicate a single MTBI has negligible long-term impacts on cognition.

Keywords: Assessment, Forensic neuropsychology, Rehabilitation

Introduction

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Animal studies identified a pathophysiological correlate of mild traumatic brain injury (MTBI) over three decades ago (Ommaya & Gennarelli, 1974). Since then, MTBI has been examined in the emergency room (Alves, Macciocchi, & Barth, 1993), single- and multi-center longitudinal studies (Dikmen, Machamer, Winn, & Temkin, 1995; Levin et al., 1987), sports (Hinton-Bayre & Geffen, 2002; Macciocchi, Barth, Alves, Rimel, & Jane, 1996; McCrea et al., 2003), and spinal cord injury

(SCI) rehabilitation (Davidoff, Morris, Roth, & Bleiberg, 1985).

Meta-analyses of controlled studies have found that a single MTBI has a moderate effect (Cohen's d = −0.41 to −0.54) on overall neuropsychological test performance 1–7 days post-injury (Belanger, Curtiss, Demery, Lebowitz, & Vanderploeg, 2005; Belanger & Vanderploeg, 2005; Schretlen & Shapiro, 2003), a small effect (d = −0.29) 7–30 days post-injury (Schretlen & Shapiro, 2003), negligible effects (d = −0.08) 30–89 days post-injury (Schretlen & Shapiro, 2003), and negligible effects (d = −0.12 to 0.04) 90 or more days post-injury (Binder, Rohling, & Larrabee, 1997; Schretlen & Shapiro, 2003).

Rohling and colleagues (2011) used a random effects meta-analytic technique to re-analyze existing outcome studies and establish effect sizes for multiple cognitive domains following MTBI. The mean effect size across all cognitive domains at 7 days post-injury was −0.39 and at 8–30 days post-injury was −0.32. At 31–92 days post-injury (mean = 58 days), the mean effect size across cognitive domains was −0.14, but moderate effects were observed for several individual domains including visual memory (−0.45), working memory (−0.34), and executive functioning (−0.32). The mean effect size at 93+ days (mean = 234 days) post-injury was −0.07 with only working memory (−0.19) showing an effect size above −0.10.

Meta-analytic techniques have provided important information on how MTBI affects cognitive functioning at various points in time post-injury, but all meta-analyses are constrained by methodological limitations in the studies selected for analysis. For example, MTBI investigations that exclude participants based on age, time from injury to assessment, co-occurring medical disorders, presence of pre-injury learning disorders, or that have high attrition can significantly reduce the generalizability of research findings to clinical practice (Corrigan et al., 2003; Luoto et al., 2013). Consequently, prospectively examining the effects of MTBI in a consecutive cohort of persons who have sustained co-occurring physical injuries and associated secondary conditions and receive standardized acute rehabilitation treatment may help address concerns about the representativeness and equivalence of MTBI and trauma control groups (Belanger et al., 2005;

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Dikmen & Levin, 1993; Rohling et al., 2011).

The traumatic SCI population has a high base rate of co-occurring MTBI (Davidoff et al., 1985, 1988; Macciocchi, Seel, Thompson, Byams, & Bowman, 2008), which provides an opportunity to study the acute effects of MTBI on cognitive functioning in a trauma cohort where the control group has equivalent physical injuries, secondary conditions, and treatment setting. Studying persons with traumatic SCI in the inpatient rehabilitation setting also allows for observation and analysis of medications and injury mechanisms that potentially contribute to lower than the expected neuropsychological test performance but are infrequently addressed in MTBI meta-analytic studies.

A number of factors other than MTBI that may explain neuropsychological test performance can also be examined in a prospective, cohort study. For instance Dikmen, Machamer, and Temkin (2001) report that socio-demographic factors are powerful predictors of low neuropsychological test performance. Moreover, pre-injury histories of low educational achievement or learning disabilities are not commonly examined in MTBI studies, despite evidence of their negative impact on test performance (Greiffenstein & Baker, 2003; Mapou, 2008).

In this prospective cohort study, we compared the neuropsychological test performance of persons who sustained traumatic SCI and documented co-occurring MTBI to a concurrent control group who sustained only a traumatic SCI. Demographically diverse participants were tested while receiving inpatient rehabilitation between 26 and 76 days post-injury, consistent with the 30–90-day post-injury epoch frequently reported in the meta-analysis literature (Rohling et al., 2011). We also examined socio-demographics, self-reported history of learning problems, markers of injury severity, and prescribed medications as potential covariates of neuropsychological test performance. Based on current research evidence from meta-analytic and standalone studies that used control groups, we hypothesized that there would be no differences in cognitive functioning between the SCI and MTBI and the SCI alone groups.

Methods

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Participants

The current sample was a subset of a larger sample of persons participating in a National Institute of Rehabilitation Research (NIDRR) funded study on traumatic SCI and co-occurring TBI (Macciocchi et al., 2008). The study was conducted at an urban, NIDRR Model Spinal Cord Injury System center that is designated as a long-term acute care hospital. Persons with a traumatic SCI aged 16–59 admitted for rehabilitation over an 18-month period (2004–2005) were eligible for inclusion (n = 266). Due to the unavailability of bilingual examiners, non-English speaking persons were excluded from the study. Eighty percent of eligible persons consented to participate (n = 212) and 89% of enrolled participants completed all inpatient admission and outcome measurement (n = 189).

Participant data for the current study were included if persons had a medically documented traumatic SCI with either no documented brain injury or a medically documented, non-complicated MTBI as evidenced by negative imaging tests but either a period of post traumatic amnesia (PTA) < 24 h or a GCS total score of 11T, 13, or 14. The initial sample contained data on 140 persons with SCI alone or SCI and co-occurring MTBI. We excluded data on persons who previously sustained brain injury (n = 11) and persons tested before 26 days (n = 6) or after 92 days (n = 6). The final sample consisted of 117 participants.

Measures

Neuropsychological tests were selected to assess diverse cognitive skills while eliminating performance confounds due to upper extremity motor impairment associated with tetraplegia. The tests administered included Wechsler Adult Intelligence Scale-3 (WAIS-3) Digit Span (DS) and Letter-Number Sequencing (LNS) Tests (Wechsler, 1997); the Hopkins Verbal Learning Test 2nd Edition (HVLT-2; Brandt & Benedict, 2001); the Symbol Digit Modalities Test-Oral (SDMT-O; Smith, 1995); the Category Test-Short Form (SCAT; Wetzel & Boll, 2000); and the Continuous Visual Memory Test (CVMT; Trahan & Larrabee, 1988). All six tests are routinely used in clinical practice

and research and have standardized administration and scoring procedures and psychometric properties, and age corrected scores.

Procedure

The current study was approved by the host institution's Research Review Committee and informed consent was obtained from participants prior to enrollment. Participants were enrolled within 1 week of SCI acute rehabilitation admission. Trained research coordinators completed a structured clinical interview of the participant and when available a family member to document selected pre-injury medical issues and risk factors for cognitive impairment. A trained research coordinator administered all six neuropsychological tests during a single testing session. The research coordinator was blinded to brain injury diagnosis at the time of testing. MTBI diagnosis was established by two investigators (SNM and RTS) based on a standardized medical record review, which was completed 6 months prior to and independent of review or analysis of neuropsychological data (Macciocchi et al., 2008).

Data Analyses

Cramer's *V* was used to compare demographics and injury characteristics of the SCI alone and SCI and MTBI groups. Analysis of covariance (ANCOVA) was used to examine differences in neuropsychological test scores between the SCI alone and the SCI and MTBI groups. Eight covariates were selected based on their potential to impact neuropsychological test performance: highest education level achieved, self-reported history of learning problems (e.g., attention deficit, reading, or spelling problems), African-American race, ASIA C5-T1 motor subscale score, days from injury to rehabilitation admission (i.e., a surrogate marker of medical acuity/physical injury severity), injury due to motor vehicle crash (MVC), injury due to violence, and prescribed narcotic medications.

Eta squared (η^2) was calculated for the ANCOVAs to identify the effect size of each of the eight covariates and the presence or the absence of MTBI controlling for all other model variables.

Covariates with $p \geq .15$ were removed one at a time from each model starting with the covariate with the highest p-value provided that removal did not change the direction or degree of the relationships between the presence of MTBI and neuropsychological test scores. Cohen's d was calculated using the standard deviation of the pooled sample to identify the effect size of MTBI versus no TBI on neuropsychological test scores. The percentage of persons with and without MTBI scoring 1.33 *SD*s below the mean or ninth percentile, 1.66 *SD*s below the mean or fifth percentile, and 2.0 *SD*s below the mean or second percentile were compared using the phi coefficient. Given the limited number of a priori between group tests for each research question, an alpha level of 0.05 was deemed appropriate.

Results

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Table 1 provides participant characteristics data. Both the SCI and SCI + MTBI groups were predominately young (range 16–56) and men (82%) with equivalent mean education levels of 12 years (range 8–20 years). The sample was predominately White and African American. The incidence of self-reported, pre-injury learning problems was <15%.

Table 1.

Characteristics of SCI and MTBI and SCI alone samples

Characteristic	Total (n = 117)	SCI + MTBI (n = 53)	SCI (n = 64)	p-value
Age (years)	27.85 ± 9.83	26.81 ± 9.87	28.70 ± 9.79	.302
Gender (men, %)	82.1	88.7	76.6	.089
Race				.420
White (%)	60.7	67.9	54.7	
African American (%)	36.8	30.2	42.2	

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Other (%)	2.6	1.9	3.1	
Education (highest # years completed)	12.22 ± 2.00	11.89 ± 1.90	12.50 ± 2.06	.099
Pre-injury learning problem (yes, %)	13.7	17.0	10.9	.344
Injury Etiology				.000
Motor vehicle accident (%)	54.7	73.6	39.1	
Violence (%)	21.4	3.8	35.9	
Sporting injury (%)	14.5	7.5	20.3	
Falls/flying object (%)	9.4	15.1	4.7	
Days from injury to rehabilitation admission	27.92 ± 14.11	30.19 ± 12.99	26.05 ± 14.81	.114
SCI motor level and completeness				.696
C1-4, ASIA grade A–C (%)	6.0	5.7	6.3	
C1-4, ASIA grade D (%)	5.1	5.7	4.7	
C5-8, ASIA grade A–C (%)	30.8	34.0	28.1	

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Notes: SCI = spinal cord injury; MTBI = mild traumatic brain injury; ASIA = American Spinal Injury Association Impairment Scale; C = cervical; T = thoracic; S = sacral; NP = neuropsychological.

All reported statistics are the mean ± SD or % of sample. Age, education, days from injury to rehabilitation admission and NP testing, and ASIA C5-T1 motor score *p*-values based on the one-way analysis of variance. Gender, race, pre-injury learning problem, injury etiology, and narcotic medication use *p*-values based on Cramer's *V*.

Participants in both the SCI alone and SCI and MTBI groups had equivalent SCI motor levels and completeness of injury. The SCI and MTBI group was more likely to be injured in a motor vehicle accident, whereas the SCI alone group was more likely to be injured as a result of violence or sporting injury. Of the participants who sustained MTBI, 93% had documented loss of consciousness lasting <30 min. PTA was present in 100% of participants with MTBI. The vast

majority of participants were prescribed narcotic medications (80%). Neuropsychological tests were administered a mean of 46 days post-injury (range 26–76 days).

ANCOVA produced models of neuropsychological test performance that had effect sizes, that is, variance explained, as high as 0.350 for LNS and as low as 0.064 on the SCAT (Table 2). Completed education level (years) was a significant covariate on the five neuropsychological tests in which education corrected norms were not available. African-American race was a significant covariate in six of the seven neuropsychological test models and approached significance ($p = .052$) in the seventh model. Self-reported history of learning problems was significant on three tests of working memory and processing speed. No significant predictors of SCAT neuropsychological test performance were identified. Controlling for covariates, sustaining MTBI did not significantly contribute to neuropsychological test performance and had an effect size (η^2) of 0.02 or less on all seven measures.

Table 2.

Parameter estimates and effect sizes for potential covariates and mild TBI on neuropsychological test scores

Tests model p, η^2	**Data reported**	**Intercept**	**Years education**	**Race**	**Learning problem**	**Prescribed narcotics**	**Days injury to rehabilitation**	**Injury due to MVC**	**Injury due to violen**
WAIS-3 LNS	*B*	6.45	0.40	−2.13	−1.97	–	–	−1.06	−1.29
$p <$ .001	95% CI	2.77, 9.94	0.14, 0.65	−3.27, −1.00	−3.33, −0.61			−2.23, 0.11	−2.95, 0.36
$\eta^2 =$ 0.350	p-value	**.001**	**.003**	**<.001**	**.005**			.076	.125
	η^2		**0.081**	**0.114**	**0.071**			0.029	0.022

WAIS-3 DS	*B*	7.79	0.36	−2.51	−2.83	−0.82	−0.13		
$p <$ .001	95% CI	4.37, 11.21	0.12, 0.59	−2.30, −0.39	−2.70, −0.09	−1.93, 0.28	−0.07, −0.00		
$\eta^2 =$ 0.252	*p*-value	**.000**	**.003**	**.006**	**.036**	.142	**.043**		
	η^2		**0.077**	**0.066**	**0.039**	0.019	**0.037**		
SDMT-Oral	*B*	49.47	–	−4.52	−5.16	–	−0.18	−3.97	−8.13
$p <$	95% CI	44.34,		−8.82,	−10.35,		−0.31, −0.06	−8.37,	−14.25

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Notes: HVLT = Hopkins Verbal Learning Test; WAIS-3 DS = Wechsler Adult Intelligence Scale-3 Digit Span; SCAT = Short Category Test; WAIS-3 LNS = Wechsler Adult Intelligence Scale-3 Letter-Number Sequencing; CVMT = Continuous Visual Memory Test; SDMT = Symbol Digit Modality Test; η^2 = eta-squared; *B* = beta coefficient; CI = confidence interval; – = covariate was not significant at $p \geq .15$ and removed from the model without changing the nature of the relationships between other variables.

ASIA C5-T1 motor subscale score was not significant in any model and was not included in Table 2. SDMT and SCAT norms control for education level. Bold values indicate $P < .05$.

Univariate comparison of neuropsychological test performance between the SCI and MTBI and SCI alone groups revealed no differences on verbal memory (HVLT Total and Delayed), working memory (DS and LNS), perceptual reasoning (SCAT), visual memory (CVMT), or processing speed (SDMT-O; Table 3). Effect sizes (Cohen's *d*) for each neuropsychological test ranged from −0.26 to 0.08 with an aggregated effect size for the overall battery of −0.16 at a mean of 46 days post-injury.

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Table 3.

Estimated marginal means (95% confidence intervals) and effect sizes (Cohen's *d*) for MTBI on neuropsychological test scores

Cognitive domains	Tests	SCI + MTBI		SCI		*F*-value	*p*-value	Pooled SD	Cohen's *d*
		Mean	95% CI	Mean	95% CI				
Verbal memory	HVLT Delayed (T)*	37.73	34.65, 40.80	40.93	38.09, 43.77	2.25	.137	12.43	−0.26
Verbal memory	HVLT Total (T)*	38.56	35.69, 41.43	41.34	38.71, 43.96	1.95	.165	11.45	−0.24
Working memory	WAIS-3 DS (SS)*	9.30	8.63, 9.98	9.89	9.28, 10.50	1.59	.210	2.73	−0.22
Perceptual reasoning	SCAT (T)*	41.54	38.61, 44.47	43.92	41.26, 46.58	1.41	.238	10.84	−0.22
Working memory	WAIS-3 LNS (SS)*	8.64	7.89, 9.39	9.30	8.62, 9.97	1.45	.232	3.04	−0.21
Visual memory	CVMT Total (T)*	39.30	34.77, 43.83	40.44	36.35, 44.53	0.13	.724	17.18	−0.07
Processing speed	SDMT-Oral (T)*	38.91	36.12, 41.70	38.06	35.54, 40.57	0.18	.669	10.73	0.08

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Notes: HVLT = Hopkins Verbal Learning Test; WAIS-3 DS = Wechsler Adult Intelligence Scale-3 Digit Span; SCAT = Short Category Test; WAIS-3 LNS = Wechsler Adult Intelligence Scale-3 Letter-Number Sequencing; CVMT = Continuous Visual Memory Test; SDMT = Symbol Digit Modality Test; CI = confidence interval; SS = scaled score; T = T-score; SD = standard deviation.

Neuropsychological test battery mean effect size, Cohen's d = 0.16.

Comparison of binary classifications of lower than expected neuropsychological test performance, that is, 1.33 *SD*s below the mean or ninth percentile, 1.66 *SD*s below the mean or fifth percentile, and 2.0 *SD*s below the mean or second percentile showed a greater percentage of persons in the SCI and MTBI group who scored 1.33 *SD*s below the mean on the WAIS-3 DS (Table 4). No other differences between the SCI and MTBI and SCI alone groups were found.

Table 4.

Percent of participants with low neuropsychological test scores in SCI and MTBI versus SCI group

Cognitive domain	Test	SD≤	% SCI + MTBI	% SCI	*p*-value
Verbal memory	HVLT Total (T)	−1.33	43.4	34.9	.351
	HVLT Total (T)	−1.66	32.1	22.2	.232
	HVLT Total (T)	−2.00	28.3	14.3	.063
	HVLT Delayed (T)	−1.33	49.1	38.7	.265
	HVLT Delayed (T)	−1.66	32.1	24.2	.347
	HVLT Delayed (T)	−2.00	30.2	21.0	.256
Working memory	WAIS-3 DS (SS)	−1.33	20.8	6.3	**.019**
	WAIS-3 DS (SS)	−1.66	9.4	1.6	.055
	WAIS-3 DS (SS)	−2.00	1.9	1.6	.893
	WAIS-3 LNS (SS)	−1.33	19.2	19.0	.980
	WAIS-3 LNS (SS)	−1.66	7.7	9.5	.729
	WAIS-3 LNS (SS)	−2.00	3.8	4.8	.811

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Visual memory	CVMT Total (T)	−1.33	45.3	35.9	.505
	CVMT Total (T)	−1.66	34.0	34.4	.963
	CVMT Total (T)	−2.00	34.0	29.7	.621
Perceptual reasoning	SCAT (T)	−1.33	40.4	34.9	.547
	SCAT (T)	−1.66	21.2	15.9	.466
	SCAT (T)	−2.00	15.4	9.5	.339

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Notes: HVLT = Hopkins Verbal Learning Test; WAIS-3 DS = Wechsler Adult Intelligence Scale-3 Digit Span; SCAT = Short Category Test; WAIS-3 LNS = Wechsler Adult Intelligence Scale-3 Letter-Number Sequencing; CVMT = Continuous Visual Memory Test; SDMT = Symbol Digit Modality Test; CI = confidence interval; SS = scaled score; T = T-score; SD = standard deviation. Bold values indicate $P < .05$.

Discussion

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Persons who sustained traumatic SCI and co-occurring MTBI did not evidence significantly greater impairment on neuropsychological tests when compared with persons who sustained a traumatic SCI alone. The aggregated MTBI effect size of −0.16 at 26–76 days post-injury in our sample is consistent with the MTBI aggregated effect size of −0.14 at 31–92 days post-injury reported by Rohling and colleagues (2011). Socio-demographic, pre-injury, and medical covariates explained more variance in neuropsychological test performance than MTBI. Consistent with previous research, education was positively associated with better neuropsychological test performance, whereas African-American race and self-reported pre-injury history of learning problems contributed to lower test performance (Dikmen et al., 2001; Greiffenstein & Baker, 2003; Mapou, 2008). Days from injury to rehabilitation admission and injury mechanism also evidenced stronger associations with neuropsychological test performance than a medically documented MTBI. Our

findings reaffirm the critical importance of using control groups sampled from the same population when studying the effects of MTBI on cognitive functioning.

We found lower than expected neuropsychological test performance in our SCI sample with and without MTBI, with mean age-corrected test scores typically falling 1 SD below normative expectations. Several factors may explain overall low test performance in our sample. First, our sample was a traumatically injured cohort and markers of severity (i.e., days from injury to rehabilitation admission) and injury etiology (i.e., MVCs or violence) showed evidence of negatively affecting cognitive test performance. Furthermore, 36.8% of persons in our study identified themselves as African American, a rate that is almost three times the estimated percentage of African Americans in the U.S. census. Based on model beta coefficients, African-American participants scored approximately 0.4–1.2 *SD*s lower on all seven neuropsychological tests, which may be attributable to unequal access to educational opportunities, cultural differences, and lack of cultural equivalence in cognitive measures (Dotson, Kitner-Triolo, Evans, & Zonderman, 2008; Manly, Jacobs, Touradji, Small, & Stern, 2002; Manly, Schupf, Tang, & Stern, 2005). Finally, the high rates of low scores found in persons with SCI alone is consistent with other recent studies demonstrating relatively high base rates of low scores in normative samples (Binder, Iverson, & Brooks, 2009).

Our data can inform clinical practice in several ways. Our findings were consistent with the existing body of evidence from controlled studies that reports a single MTBI has limited effects on cognitive functioning at 30–89 days post-injury. Our analyses also demonstrate that pre-injury, demographic, and medical factors explain more variance in neuropsychological test scores than MTBI. Clinicians must consider pre-injury learning problems and co-occurring trauma as potential contributors to lower than expected neuropsychological test performance following MTBI. Considering race, ethnicity, culture, and education is also essential in post-MTBI test score interpretation. Lastly, using lower than expected neuropsychological test scores as the primary basis for diagnosing MTBI >30 days post-injury will likely result in high rates of false positive diagnoses.

Our study has several methodological strengths and limitations. Participants with and without MTBI

were enrolled from a consecutive, demographically diverse sample of persons with SCI who had equivalent age, education, gender, motor level and completeness of injuries, days from injury to rehabilitation, medications, and rehabilitation treatment, which minimized the potential bias in post-injury environmental factors and non-equivalence of the comparison group. Acute medical records were rigorously retrieved and reviewed using a standardized diagnostic algorithm to determine the history of MTBI prior to examining covariates or neuropsychological test data. The percentage of persons diagnosed with TBI in our initial SCI study was the highest rate reported in an inpatient SCI rehabilitation sample (Macciocchi et al., 2008). The consent rate was high (80%) and the attrition rate was quite low (11%). Finally, the socio-demographic and injury-related covariates examined provide empirically plausible alternative explanations for lower than expected neuropsychological test performance in the SCI population.

With regard to study limitations, persons with SCI often have risk factors for reduced cognitive efficiency including depression, pain disorders, and insomnia (Sipski & Richards, 2006), which we were unable to systematically examine, but merit exploration in future MTBI studies. We did not conduct effort testing, which may have identified suboptimal effort as a covariate of lower than expected test performance in both the SCI and SCI + MTBI groups. Suboptimal effort can lower test performance by at least 1 *SD* (Green, Rohling, Lees-Haley, & Allen, 2001). Future studies of MTBI using trauma populations should consider using effort measures to exclude suboptimal effort as an explanation for lower than expected test scores. Our sample was predominately young, that is, <40 years old, and our results cannot be generalized to older persons with MTBI. Our sample also was not large but generated models with high power. Lastly, eta-squared and Cohen's *d* are effect size calculations for samples and are not corrected for populations.

In conclusion, few controlled studies have been conducted in populations with an MTBI and other significant trauma during the acute recovery period. We found no evidence that a single MTBI negatively impacted cognitive functioning following co-occurring SCI. These results support prospective, controlled studies conducted over the past two decades (Rohling et al., 2011). Further research on the impact of physical trauma and secondary conditions on neuropsychological test

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performance is warranted. The evidence from this study and the research literature indicate that clinicians who observe lower than expected neuropsychological test performance >30 days following a single MTBI must consider alternative explanations for test performance including socio-demographic factors, history of learning disorders, and co-occurring medical conditions.

Funding

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Conflict of Interest

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None declared.

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Multiple Concussions and Neuropsychological Functioning in Collegiate Football Players

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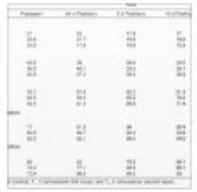
Abstract and Figures

OBJECTIVE: To document neurocognitive and neurobehavioral consequences of 1 versus 2 concussions. DESIGN AND SETTING: Nonequivalent, pretest-posttest cohort design with multiple dependent measures. Participants were selected from a large sample of athletes who participated in a comprehensive, multiuniversity study of football-related concussion. SUBJECTS: College football players who sustained 1 and 2 grade 1 concussive injuries were matched for age, education, and duration of competitive football. MEASUREMENTS: Neuropsychological tests and symptoms checklists. RESULTS: Multivariate analysis of variance did not show a statistically significant difference in test performance between players with 1 or 2 concussions. Chi square analyses revealed that concussions significantly increased the number of symptom complaints, but symptoms returned to baseline by 10 days postinjury. The effects of 2 injuries did not appear to be significantly greater than that of a single injury. Differences in response to concussion were observed. CONCLUSIONS: Neurocognitive and neurobehavioral consequences of 2 concussions did not appear to be significantly different from those of 1 concussion, but methodologic issues place limitations on data interpretation. Additional studies are needed to clarify the neuropsychological consequences of multiple concussions.



. Test Scores in Players With 1…

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Multiple Concussions and Neuropsychological Functioning in Collegiate Football Players

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Objective: To document neurocognitive and neurobehavioral consequences of 1 versus 2 concussions.

Design and Setting: Nonequivalent, pretest-posttest cohort design with multiple dependent measures. Participants were selected from a large sample of athletes who participated in a comprehensive, multiuniversity study of football-related concussion.

Subjects: College football players who sustained 1 and 2 grade 1 concussive injuries were matched for age, education, and duration of competitive football.

Measurements: Neuropsychological tests and symptoms checklists.

Results: Multivariate analysis of variance did not show a statistically significant difference in test performance between players with 1 or 2 concussions. Chi square analyses revealed that concussions significantly increased the number of symptom complaints, but symptoms returned to baseline by 10 days postinjury. The effects of 2 injuries did not appear to be significantly greater than that of a single injury. Differences in response to concussion were observed.

Conclusions: Neurocognitive and neurobehavioral consequences of 2 concussions did not appear to be significantly different from those of 1 concussion, but methodologic issues place limitations on data interpretation. Additional studies are needed to clarify the neuropsychological consequences of multiple concussions.

Key Words: sports injuries, neuropsychological tests, symptoms

Over the past 15 years, research pertaining to concussive injuries sustained during athletic endeavors has increased substantially.[1] Findings from these studies have been generally consistent and suggest that concussive injuries in competitive American football can cause time-limited neuropsychological and neurobehavioral problems.[2–4] Although 1 concussion does not appear to result in significant morbidity, the effect of multiple concussions is less clear. In a recent study,[4] a posttest-only control group design was used to compare athletes who had a history of 1 concussion with athletes who had a history of 2 or more concussions. The authors found that athletes who sustained 2 or more concussions to prospectively examine the neurobehavioral and neuropsychological consequences of 2 concussive injuries. Players who sustained 2 concussions were compared with players who sustained 1 concussion using a nonequivalent, pretest-posttest comparison design. Players who sustained 1 concussion were used as controls in order to contrast the effects of 1 versus 2 concussions. As mentioned previously, several studies have shown that a single concussion is associated with time-limited neurocognitive impairment. As such, identifying neurocognitive impairment was not the primary focus of our investigation. The primary goal was to determine if a second concussion produced identifiable cognitive deficits above and beyond

sions reported more neurobehavioral symptoms and had more impairment on selected neuropsychological tests than athletes who had a history of a single concussion. Despite the differences on some neuropsychological measures, athletes with a history of 1 versus 2 or more concussions did not differ on tests of auditory attention, verbal fluency, verbal learning, verbal memory, or fine motor dexterity.[4] In addition, players with 2 or more concussions were aggregated, and the effect of different numbers of concussions was not specified.[4]

Most studies investigating the effects of single or multiple concussions have been retrospective investigations using post-test-only designs.[1] Accordingly, we designed our investigation

those observed after a single injury. Based on prior investigations, we hypothesized that players who sustained 2 concussions would evidence significantly greater neurocognitive dysfunction and postconcussive symptoms compared with players who sustained a single injury.

METHODS

Subjects

Participants in this study (n = 24) were selected from a larger sample of athletes who participated in a comprehensive

study of concussive injury in Division I-A collegiate football players. In the initial study, 2300 players were prospectively examined and followed for 4 years to determine the neuropsychological consequences of concussive injuries. During the study period, 195 players sustained grade 1 concussions based on contemporary classification guidelines.[1] Six percent of all players with documented concussions sustained 2 injuries (n = 12). Five of these athletes sustained concussions in the same year (mean separation, 33 days; range, 14 to 70 days), while 7 players sustained concussions in consecutive years (mean separation, 532 days; range, 364 to 686 days). Players who sustained 2 concussions (T_2) were compared with a selected cohort of players who sustained a single concussion (S). Players sustaining 1 concussion were selectively matched with players sustaining 2 concussions based on age, education, years in competitive football, and prior concussion history (none). Players with a single concussion (S) had a mean age of 19.5 years and a mean 8.4 years of experience in competitive football, and players with 2 concussions (T_2) had a mean age of 19.1 years and a mean 9.1 years of experience in competitive football.

METHODS

All players (n = 24) were assessed preseason to establish baseline functioning. In addition to completing a physical ex-

MANOVA was used to compare scores of players experiencing 2 injuries after their first (T_1) and second (T_2) injuries to determine if a second concussion produced a change in cognitive functioning. Additionally, players who were injured twice in close temporal proximity (mean separation, 33 days) were compared with players who sustained 2 injuries over 2 or more seasons (mean separation, 532 days). Finally, preseason and postseason scores of players with 2 injuries were compared using a within-subjects MANOVA to examine changes over time.

Mean test scores for each group are presented in Table 1. The MANOVA analysis revealed that the test results of players with a single injury (S) did not differ significantly from those of players who sustained 2 injuries, either at the time of their first injury (T_1: $F = 4.2$, $P < .06$) or second injury (T_2: $F = 1.09$, $P < .386$). Within-subjects comparison of players who sustained 2 injuries after their first injury (T_1) and second injury (T_2) revealed no significant differences in test performance ($F = 0.858$, $P < .514$). Comparison of players' preinjury test scores with postseason performance after their second injury revealed a trend toward improved performance ($F = 3.27$, $P < .108$). When the group sustaining 2 concussions was analyzed separately, no differences were noted in test performance between players who sustained injuries in close proximity or in successive seasons ($F = 1.12$, $P < .351$).

Players' self-reported symptoms (headache, dizziness, and

amination, players completed several neuropsychological measures, including the Paced Auditory Serial Addition Task (Brainmetric Software, Marlton, NJ),[5] the Trail-Making Tests A and B from the Halstead-Reitan Neuropsychological Test Battery (Reitan Neuropsychological Laboratory, Tucson, AZ),[6] and the Symbol Digit Test (Psychological Assessment Resources, Inc, Odessa FL).[7] These tests were designed to measure various aspects of visual and auditory attention as well as information processing speed. Psychometrics of these instruments can be obtained from various sources.[8] Players also completed a history questionnaire and a symptom checklist.

Players who were suspected of sustaining head injuries during practices or games were examined by certified athletic trainers and physicians using standardized medical and mental status procedures. Players' temporal and spatial orientation and short-term memory were systematically assessed after injury. Players failing items requiring intact orientation and memory were considered to have sustained a concussion and were continuously assessed until resolution of posttraumatic confusion. No players in our study experienced a documented loss of consciousness or posttraumatic confusion lasting longer than 30 minutes, which is consistent with a grade 1 concussion using the American Academy of Neurology and Virginia Neurologic Institute Standards.[1] Players who failed the mental status examination were then assessed at 24 hours, 5 days, and 10 days postinjury using the neuropsychological measures administered during the baseline assessment. Neuropsychological tests were administered by research staff trained in test administration.

RESULTS

Neuropsychological test scores and self-reported symptoms of players who sustained 2 injuries (T_2) were compared with test scores and symptoms of players who sustained a single injury (S) using a between-subjects multivariate analysis of variance (MANOVA). In addition, a within-subjects

memory loss) were summed before completing the analyses (Table 2). Statistical examination of the total number of symptoms using χ^2 analyses revealed a significant effect for time. Both groups (S and T_1) had a statistically significant increase in the number of players with symptoms (headache, dizziness, and memory loss) at 24 hours postinjury ($\chi^2_4 = 22$, $P < .001$) and 5 days postinjury ($\chi^2_4 = 40$, $P < .001$). In contrast, the number of players with symptoms at 10 days postinjury was not significantly different from the number with symptoms preseason ($\chi^2_4 = 0.20$, $P < .50$). Analyses of symptoms with respect to groups revealed significant differences in symptom reports (headache, dizziness, and memory loss) between group S (single injury) and group T_1 after their first injury ($\chi^2_2 = 10.6$, $P < .005$). Players who sustained 2 injuries did not evidence statistically significant differences in symptom reports after first injuries (T_1) and second injuries (T_2) ($\chi^2_2 = 1.41$, $P < .50$). The proportion of patients reporting symptoms also did not differ for players sustaining injuries in close proximity and players sustaining more remote injuries.

DISCUSSION

Our analyses suggest that 2 grade 1 concussive injuries sustained at least 2 weeks apart during competitive American football did not result in significantly more neurocognitive impairment than a single concussive injury. Compared with players who sustained a single injury, players who sustained 2 injuries performed as well as or better on all neuropsychological tests after their first and second concussions. In addition, after a second concussion, there was no evidence of a decrement in test performance relative to the performance observed after players' first concussions. Furthermore, players who sustained 2 concussions performed better on postseason assessments than on preseason examinations.

Analyses of self-reported symptoms revealed a significant effect for time after injury. The number of players reporting symptoms increased significantly after 1 or 2 injuries, but

Table 1. Test Scores in Players With 1 versus 2 Mild Head Injuries*

Test	Time				
	Preseason	24 h Postinjury	5 d Postinjury	10 d Postinjury	Postseason
Trail-Making A					
S	21	22	17.9	17	NA†
T_1	22.8	21.7	18.8	18.6	NA
T_2	22.8	17.6	16.9	15.9	16.6
Trail-Making B					
S	46.8	39	39.8	34.5	NA
T_1	50.5	40.1	35.2	36.1	NA
T_2	50.5	37.4	30.3	29.9	32.9
Symbol Digit					
S	55.7	57.8	62.2	61.3	NA
T_1	62.5	59.2	65.9	70.0	NA
T_2	62.5	61.5	68.8	71.4	71.4
Paced Auditory Serial Addition Task 3					
S	77	81.9	96	88.4	NA
T_1	82.5	86.7	94.4	93.8	NA
T_2	82.5	92.1	96.0	94.6	94.3
Paced Auditory Serial Addition Task 4					
S	65	62	78.5	88.1	NA
T_1	72.4	77.1	90.8	88.1	NA
T_2	72.4	86.6	90.2	93	88.4

*S indicates 1 concussion (control); T_1, 2 concussions (first injury); and T_2, 2 concussions (second injury).
†Not available.

Table 2. Number of Players Reporting Postconcussive Symptoms*

Time	No. Reporting Headache			No. Reporting Dizziness			No. Reporting Memory Loss		
	S	T_1	T_2	S	T_1	T_2	S	T_1	T_2
Preseason	4	3	3	1	1	1	1	1	1
24 h postinjury	8	4	5	2	3	4	2	2	4
5 d postinjury	4	8	7	0	4	5	2	3	3
10 d postinjury	4	2	4	0	2	2	2	1	0

*S indicates 1 concussion (control); T_1, 2 concussions (first injury), and T_2, 2 concussions (second injury).

symptom reports essentially returned to baseline by 10 days postinjury in both groups. The most commonly reported symp-

er players who experience prominent self-reported symptoms after a concussion are at greater risk for a second concussion.

tom in both groups was headache, but players who sustained 2 concussions reported more symptoms after their first and second concussions when compared with players who sustained a single concussion. Despite the presence of a differential response to the first injury, the frequency of players' symptoms after first and second injuries revealed no statistically significant increase in symptoms after a second injury, whether this injury occurred in close proximity to the first injury or at a more remote time. In other words, even though one group of players experienced more symptoms after their first injury, the responses to their first and second concussions were remarkably similar. Although interesting, the significance of these findings is not entirely clear. Differences in symptom reports could be due to normal variations in injury response accentuated by selective matching. In the future, variability in symptom reports after injury can be examined to assess whether this interaction between the first and second injuries. Most importantly, even though we observed no differences between players with proximal versus remote injuries, our sample was too small to definitively answer questions about injury proximity. Finally, none of our players sustained more than 2 concussions, which limits direct comparison with studies assessing players with as many as 10 concussions.[4]

In addition to sample size, injury frequency, and the timing of injuries, test sensitivity issues require comment. For example, a number of neuropsychological tests are susceptible to practice effects.[10] In our study, players who were injured twice were exposed to all tests on at least 7 occasions. Actually, despite being injured, players evidenced improved performance over time regardless of testing time (24 hours, 5 days, 10 days) or injury status (1 or 2 concussions). As such, the genuine neurocognitive consequences of concussions may be obscured by considerable exposure to tests. Of course, an injury with serious neuropsychological consequences would most likely reduce the influence of practice effects, but there was no evidence of a significant decline in neuropsychological test performance for any player in our sample.

A final issue deserving attention is the effect of group re-

Despite our findings, several methodologic issues merit discussion. First, the base rate of documented multiple injuries in our sample was quite low (6%).[3] As such, our data are based on a small sample of players who may not adequately represent the population of players who typically sustain multiple injuries. Second, all of our players sustained grade 1 concussions by contemporary classification standards.[9] Although the effect of injury severity is generally consistent across players, the cumulative effects of more severe injuries are unknown. Third, the timing of injuries in our study was variable. For example, only 2 players experienced a second injury within 2 weeks of their first injury. In fact, 7 players did not even sustain both injuries in the same year but rather within 12 to 24 months. Because neurocognitive impairment and neurobehavioral symptoms after 1 concussion resolve rather rapidly,[2–4] the extended time between injuries may have limited the generalization of these data to populations in whom injuries may be more frequent, may occur in closer temporal proximity, or may be more severe. Nonetheless, as documented by other studies, our data do suggest that self-reported symptoms may be sensitive indicators of postinjury neuropsychological impairment.[2] As such, the presence of symptoms should be given serious consideration in return-to-play decisions, regardless of neuropsychological test performance.[1] In any case, further research is needed to more closely examine the effect of multiple concussions on neuropsychological function. Until then, we can have modest confidence in the fact that, although undesirable, 2 grade 1 concussions occurring at least 2 weeks apart did not appear to produce significantly greater impairment than a single injury, at least in this population of collegiate football players.

ACKNOWLEDGMENTS

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REFERENCES

search on individual responses to concussion. For example, neurocognitive test data and symptom reports document variability in response to concussions with apparently equivalent clinical features such as duration of posttraumatic amnesia. In other words, the group that experienced 2 concussions did report more symptoms after their first injury, and this reporting continued after their second concussion. Consequently, group studies using aggregated data may obscure differential responses to and recovery from injury. In order to address this issue, investigators have recently recommended using reliable change indexes (RCIs) when conducting research.[11] RCIs are calculated using preinjury and postinjury scores, with mathematical consideration given to the standard error measurement and test reliability. In essence, RCI is a type of effect size. Calculating effect sizes of injuries for individual players may yield information that would be lost when summing group data. For example, players with large injury effects can be examined independently for relationships among injury severity, neurocognitive functioning, and neurobehavioral symptoms.

In spite of the study's limitations, our data suggest that 2 concussions do not result in a statistically or clinically significant increase in neurocognitive deficits relative to a single concussion. There is also no compelling evidence that self-reported symptoms are more common or severe after a second injury. Unfortunately, methodologic limitations do not permit

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Citations (115) References (13)

... The most common acute symptoms of concussion are headaches, dizziness, fatigue, irritability, and confusion (Daneshvar, Nowinski, McKee, & Cantu, 2011;McCrory et al., 2017). Neurocognitive deficits often include attention, information processing speed, memory, and executive functioning (Collins et al., 1999;Macciocchi, Barth, Alves, Rimel, & Jane, 1996; Macciocchi, Barth, Littlefield, & Cantu, 2001; McCrea et al., 2003). These clinical impairments can translate to functional difficulties with skill acquisition and performance (Van Vleet et al., 2016). ...

... Risk factors for sport-related concussion include history of concussion Lynall, Mauntel, Padua, & Mihalik, 2015; Macciocchi et al., 2001; McCrory et al., 2017;Nordström, Nordström, & Ekstrand, 2014), fatigue (Finnoff, Jelsing, & Smith, 2011), and pre-existing pathology or psychological distress such as depression or anxiety (Fann et al., 2002;Vassallo, Proctor-Weber, Lebowitz, Curtiss, & Vanderploeg, 2007). Fann and colleagues (2002) examined injury prevalence risks associated with psychiatric illness and found increased rates of concussion in individuals who had been treated in the past year (including medication and mental health services). ...

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... For adolescents with concussion, mental health issues compound matters due to the significant cognitive development and psychosocial and emotional growth that occurs concurrently [5]. The potential cumulative or long-term deleterious effects of concussions are worrisome [6][7][8][9] [10] [11], as repeated concussions may be related to degenerative neurological conditions later in life [12][13][14]. Of equal concern, the adolescent years are often marked by engagement in alcohol and drug use, both of which may influence the incidence and outcomes of all forms of TBI. ...

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January 2005 · Neurosurgery

Mark R Lovell · Elliot J Pellman · David C. Viano · [...] · Andrew M Tucker

The National Football League (NFL) neuropsychological testing program is reviewed, and neuropsychological test data are presented on various samples of NFL athletes who sustained concussion (mild traumatic brain injury, MTBI). This study evaluated post-MTBI neuropsychological testing of NFL players from 1996 to 2001. All athletes completed a standardized battery of neuropsychological tests and ... [Show full abstract]

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Genetic polymorphisms, concussion risk, and post concussion neurocognitive deficits in college and h...

March 2013 · British Journal of Sports Medicine

Thomas R Terrell · Roberd M. Bostick · Jeffery Barth · [...] · Kenneth Michael Bielak

Objective To investigate associations of APOE and Tau gene polymorphisms with sports-related acute concussions and baseline to post-concussion neuropsychological test score changes. Design Multi-center prospective cohort study. Setting Scholarship athletes at 21 universities and 4 high schools Participants: 3218 athletes playing football (70%) or soccer (23%). Assessment of Risk Factors APOE, ... [Show full abstract]

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